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Janet M. McNicholas, Ph.D. McAndrews, Held & Malloy, Ltd. 34th Floor 500 West Madison Chicago, IL 60661			HADDAD, MAHER M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)	
	10/816,276	BETTER ET AL.	
Office Action Summary	Examiner	Art Unit	
	Maher M. Haddad	1644	
- The MAILING DATE of this communication appe Period for Reply	ears on the cover sheet with the c	orrespondence address	
A SHORTENED STATUTORY PERIOD FOR REPLY WHICHEVER IS LONGER, FROM THE MAILING DA  - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication.  - If NO period for reply is specified above, the maximum statutory period with a property of the period for reply within the set or extended period for reply will, by statute, any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	TE OF THIS COMMUNICATION 6(a). In no event, however, may a reply be timil apply and will expire SIX (6) MONTHS from cause the application to become ABANDONE	l.  lely filed  the mailing date of this communication.  O (35 U.S.C. § 133).	
Status			
1)⊠ Responsive to communication(s) filed on <u>24 Juli</u> 2a)□ This action is <b>FINAL</b> . 2b)⊠ This allowant closed in accordance with the practice under Expression is the practice of the	action is non-final. ce except for formal matters, pro		
Disposition of Claims			
4)  Claim(s) 1-38 is/are pending in the application.  4a) Of the above claim(s) 1-30,37 and 38 is/are  5)  Claim(s) is/are allowed.  6)  Claim(s) 31-36 is/are rejected.  7)  Claim(s) is/are objected to.  8)  Claim(s) are subject to restriction and/or  Application Papers  9)  The specification is objected to by the Examiner  10)  The drawing(s) filed on is/are: a) acceed to the composite of the composite	election requirement.	e 37 CFR 1.85(a). ected to. See 37 CFR 1.121(d).	
Priority under 35 U.S.C. § 119			
12) Acknowledgment is made of a claim for foreign a) All b) Some * c) None of:  1. Certified copies of the priority documents 2. Certified copies of the priority documents 3. Copies of the certified copies of the priori application from the International Bureau * See the attached detailed Office action for a list of	s have been received. s have been received in Application ity documents have been received (PCT Rule 17.2(a)).	on No ed in this National Stage	
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Attachment(s)  1) Notice of References Cited (PTO-892)  2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date	4)  Interview Summary Paper No(s)/Mail Da 5)  Notice of Informal P 6)  Other:		

Application/Control Number: 10/816,276 Page 2

Art Unit: 1644

## **DETAILED ACTION**

1. Claims 1-38 are pending.

2. Applicant's election without traverse of Group IV, claims 31-36 drawn to a method for treating a mammal suffering from an EP-CAM mediated disease, disorder or condition comprising administering the human engineered anti-EP-CAM antibody and SEQ ID NO: 21 as the species filed on 7/24/06, is acknowledged.

Upon reconsideration the Examiner has extended the search to cover SEQ ID NO: 19, 6, 8, 35, 37, 39, 41, 43 and 45.

- 3. Claims 1-30 and 37-38 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
- 4. Claims 31-36 are under examination as they read on a method for treating a mammal suffering from an EP-CAM mediated disease, disorder or condition comprising administering the human engineered anti-EP-CAM antibody and SEQ ID NO: 21, 19, 6, 8, 35, 37, 39, 41, 43 and 45.
- 5. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figures 5 and 7, on page 9,  $\P$  31 and 33 has describe several amino acid of the ING-1  $V_H$  and  $V_L$  chains that each must have a sequence identifier. Correction is required.
- 6. Claims 31-33 are objected to because it depends from non-elected base claims 1-3, respectively.
- 7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

  The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
- 8. Claims 31-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating adenocarcinomas comprising administering a pharmaceutically effective amount of the human engineered anti-Ep-CAM antibody, said antibody comprises:

the  $V_H$  of SEQ ID NO: 19 and  $V_L$  of SEQ ID NO: 6, or the  $V_H$  of SEQ ID NO: 21 and  $V_L$  of SEQ ID NO: 8, the method further comprises administering a chemotherapeutic agent,

does not reasonably provide enablement for a method for treating a mammal suffering from any "Ep-CAM mediated disease, disorder or condition" comprising administering a pharmaceutically effective amount of the human engineered anti-Ep-CAM antibody comprising a heavy chain

Art Unit: 1644

variable region comprising the amino acid sequence of SEQ ID NO: 19 or 21, in claim 31 or comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:6, 8, 35, 37, 39, 41, 43 or 45 in claim 32, or comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6 in claim 33, the method further comprising administering a chemotherapeutic agent before, after or simultaneously with the human engineered anti-Ep-CAM antibody in claim 34-36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is unlikely that human engineered anti-Ep-CAM antibody as defined by the claims which may contain either heavy or light chain variable region of an Ep-CAM antibody have the required binding function. The specification provides no direction or guidance regarding how to produce the human engineered anti-Ep-CAM antibodies as broadly defined by the claims. It is not clear for the specification as to which sequences of the heavy and light chain variable regions make an intact antibody.

At issue is the "Ep-CAM mediated disease, disorder or condition", the specification ¶22 discloses that a use of an anti-Ep-CAM antibody in the manufacture of a medicament for the treatment of a mammal with an Ep-CAM mediated disease, disorder or condition. An Ep-CAM mediated disease disorder or condition includes a carcinoma and/or metastasis of a cancer cell. Carcinomas include adenocarcinomas. However, besides the adhenocarcinomas, the specification provides insufficient guidance for Ep-CAM mediated disease, disorder or condition.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Art Unit: 1644

9. Claims 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for treating adenocarcinomas comprising administering a pharmaceutically effective amount of the human engineered anti-Ep-CAM antibody, said antibody comprises:

the V<sub>H</sub> of SEQ ID NO: 19 and V<sub>L</sub> of SEQ ID NO: 6, or

the  $V_H$  of SEQ ID NO: 21 and  $V_L$  of SEQ ID NO: 8, the method further comprises administering a chemotherapeutic agent.

Applicant is not in possession of a method for treating a mammal suffering from any "Ep-CAM mediated disease, disorder or condition" comprising administering a pharmaceutically effective amount of the human engineered anti-Ep-CAM antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 or 21, in claim 31 or comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:6, 8, 35, 37, 39, 41, 43 or 45 in claim 32, or comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6 in claim 33, the method further comprising administering a chemotherapeutic agent before, after or simultaneously with the human engineered anti-Ep-CAM antibody in claim 34-36.

Applicant has disclosed only the use of heMAb to treat adenocarcinomas; therefore, the skilled artisan cannot envision all the contemplated Ep-CAM mediated disease, disorder, or condition possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3<sup>rd</sup> column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath

Art Unit: 1644

at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See <u>University of California v. Eli Lilly and Co.</u> 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (el) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
- 35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).
- 11. Claim 31-33 are rejected under 35 U.S.C. 102(a) as being anticipated by XOMA A Leader in Therapeutic Antibodies, May 2002, as is evidence by the specification on ¶6, 17 and 74.

XOMA teaches a method for treating patients with advanced adenocarcinomas of the breast, GI tract (colorectal, pancreatic, gastric, esophageal), lung, ovary and prostate refractory comprising administering a human engineered ING-1 (heMab) monoclonal antibody (see the entire document).

While the prior art teachings may be silent as to the specific sequences of heMab per se; the method, the product used in the reference method are the same as the claimed method. Therefore providing the specific sequences of the heMab is considered inherent properties.

As is evidenced by the specification on ¶17 that the human engineered anti-Ep-CAM antibody may have a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 or SEQ ID NO: 21 and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, or SEQ ID NO: 45. The antibody comprises a variable region amino acid sequence modified to include one or more additional low risk changes and/or to include one or more additional moderate risk changes. Such variants will normally have a binding affinity for

Art Unit: 1644

human Ep-CAM which is similar to that of the mouse-human chimeric antibody ING-1 as produced by cell line HB9812. Further evidence on ¶ 6 that the ING-1 antibody is a mouse-human chimeric version of Br-1 and was previously developed and expressed in Sp2/0 cells using vectors pING2207 encoding the mouse-human chimeric ING-1 light chain mammalian and pING2225 encoding the mouse-human chimeric ING-1 heavy chain (see, e.g., U.S. Pat. No. 5,576,184) (i.e., Transfected hybridoma Sp2/0 pING22071C5.B7-pING22253F2.G6 (C499) (ATCC accession #HB9812)). The mouse-human chimeric ING-1 antibody as produced by cell line HB9812 (see ¶74).

The reference teachings anticipate the claimed invention.

12. Claim 31-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Better et al, May 2002, as is evidence by the specification on ¶6, 17 and 74.

Better et al teach that recombinant human engineered ING-1 monoclonal antibody, ING-1(heMAb), exhibits minimal immunogenicity in patients with advanced adenocarcinomas. Better further teaches that a method of treating advanced adenocarcinomas comprising administering the murine anti-EpCAM antibody Br-1 was modified to be less immunogenic in man. Better et al teach that 13 sufrace exposed amino acid residues in the murine heavy chain variable region and 6 in the murine light cahin variable region were modified to human residues in positions unlikely to adversely affect either antigen binding or proein folding. Synthetic genes ontaining the modified variable regions linked to human IgG1 and kappa constant region cDNA were introduced into CHO-K1 cells and the immunogenicity of the recombinant product, ING-1(heMAb), was subsequently evaluated in a phase I study of patients with advanced adenocarcinomas (see Abstract).

While the prior art teachings may be silent as to the specific sequences of heMAb per se; the method, the product used in the reference method are the same as the claimed method. Therefore providing the specific sequences of the heMAb is considered inherent properties.

As is evidenced by the specification on ¶17 that the human engineered anti-Ep-CAM antibody may have a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 or SEQ ID NO: 21 and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, or SEQ ID NO: 45. The antibody comprises a variable region amino acid sequence modified to include one or more additional low risk changes and/or to include one or more additional moderate risk changes. Such variants will normally have a binding affinity for human Ep-CAM which is similar to that of the mouse-human chimeric antibody ING-1 as produced by cell line HB9812. Further evidence on ¶ 6 that the ING-1 antibody is a mouse-human chimeric version of Br-1 and was previously developed and expressed in Sp2/0 cells using vectors pING2207 encoding the mouse-human chimeric ING-1 light chain mammalian and pING2225 encoding the mouse-human chimeric ING-1 heavy chain (see, e.g., U.S. Pat. No. 5,576,184) (i.e., Transfected hybridoma Sp2/0 pING22071C5.B7-pING22253F2.G6 (C499)

Art Unit: 1644

(ATCC accession #HB9812)). The mouse-human chimeric ING-1 antibody as produced by cell line HB9812 (see ¶74).

Page 7

The reference teachings anticipate the claimed invention.

13. Claim 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Ammons et al(2001), as is evidence by the specification on ¶6, 17 and 74.

Ammons et al teach the use of ING-1(heMAb), a human engineered antibody to Ep-CAM kills tumor cells in vivo. Ammons et al teach that the in vivo efficacy of ING-1(heMAb) was evaluated in nude mice inoculated subcutaneously with 3X106 MCF-7 breast tumor cells. Starting twenty-hous later, groups of 10 mice received ING-1(heMAb) or vehicle IP, 3 times per week for 3 weeks. By day 10, mice treated wit ING-1(heMAb) had significantly lower tumor volumes than those treated with vehicle. Ammons further teaches that mice treated with 10, 30, 100 mg/kg (ING-1(heMAb) had 80%, 91% and 68% reductions in tumor volum, respectively, compared to the control group. Ammons teaches that ING-1(heMAb) has potent anti-tumor activity in vivo (see abstract in particular).

While the prior art teachings may be silent as to the specific sequences of heMab per se; the method, the product used in the reference method are the same as the claimed method. Therefore providing the specific sequences of the heMab is considered inherent properties (see the entire document).

As is evidenced by the specification on ¶17 that the human engineered anti-Ep-CAM antibody may have a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 or SEQ ID NO: 21 and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, or SEQ ID NO: 45. The antibody comprises a variable region amino acid sequence modified to include one or more additional low risk changes and/or to include one or more additional moderate risk changes. Such variants will normally have a binding affinity for human Ep-CAM which is similar to that of the mouse-human chimeric antibody ING-1 as produced by cell line HB9812. Further evidence on ¶ 6 that the ING-1 antibody is a mouse-human chimeric version of Br-1 and was previously developed and expressed in Sp2/0 cells using vectors pING2207 encoding the mouse-human chimeric ING-1 light chain mammalian and pING2225 encoding the mouse-human chimeric ING-1 heavy chain (see, e.g., U.S. Pat. No. 5,576,184) (i.e., Transfected hybridoma Sp2/0 pING22071C5.B7-pING22253F2.G6 (C499) (ATCC accession #HB9812)). The mouse-human chimeric ING-1 antibody as produced by cell line HB9812 (see ¶74).

The reference teachings anticipate the claimed invention.

Art Unit: 1644

14. Claim 31-33 are rejected under 35 U.S.C. 102(e1) as being anticipated by US 20030203447.

Page 8

The `447 publication teaches the therapeutic uses of anti-Ep-CAM antibody involving diseases, disorders or conditions related to the expression of Ep-CAM, including for use with Ep-CAM-positive tumor cells, particularly the metastasis of Ep-CAM positive tumor cells. ING-1 antibody product refers to and includes an antibody heavy comprising claimed SEQ ID NO: 19 or 21 and/or light chain protein of claimed (SEQ ID NO:6, 8, 35, 37,, 39, 41, 43 or 45 comprising at least an antibody variable region wherein the heavy and/or light chain variable region binds to Ep-CAM (see ¶ 106 and Example 6, published SEQ ID NO: 23(19) and 25(21), 10(6), 12(8), Example 11, SEQ ID NO: 39(35), 41(37), 43(39), 45(41), 47 (43) or 49(45). in particular).

The reference teachings anticipate the claimed invention.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20030203447, XOMA, Better et a; <u>OR</u> Ammons et al, each in view of WO 01/07082.

The teachings of US 20030203447 publication, XOMA, Better et al and Ammons et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the method further comprising administering a chemotherapeutic agent before, after or simultaneously with the human engineered anti-Ep-CAM antibody in claims 34-36.

The WO '082 teaches that it has been found that pre-treatment with a drug, for example a chemotherapeutic agent known to block cell cycle progression at S and/or G2/M results in a significant increase in the density of the Ep-CAM antigen population and thus in greater targeting of anti-Ep-CAM antibodies to Ep-CAM expressing tumors. The '082 publication further teaches that the perturbation of tumor cell phenotype has a significant impact on the biological effectiveness of therapeutic antibodies, and provides synergistic benefit to standard chemotherapeutic regiments. Also the '082 publication teaches that this increase in Ep-CAM

Art Unit: 1644

antigen expression appears to be tumor specific. In other wards, pre-treatment with chemotherapeutic agents that block the cell cycle at S and/or Gs/M does not seem to affect Ep-CAM antigen expression in non-tumor cells. (see page 3, line 32 to page 4, line 9 in particular). The '082 publication teaches that examples of chemotherapeutic agents which are capable of arresting Ep-CAM antigen expressing cells in G2/M are vinorelbine, cisplatin, mytomycin, paclitaxel, carboplatin, oxaliplatin and CPT-II (see page 5, lines 10-13 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to pre-treat the Ep-CAM expressing tumors with a drug such as a chemotherapeutic agent taught by the '082 publication.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so to block cell cycle progression at S and/or G2/M results in a significant increase in the density of the Ep-CAM antigen population and thus in greater targeting of anti-Ep-CAM antibodies to Ep-CAM expressing tumors. Further because pre-treatment with chemotherapeutic agents that block the cell cycle at S and/or Gs/M does not seem to affect Ep-CAM antigen expression in non-tumor cells.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

## 17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 30, 2006

Maker M. Haddad Maher Haddad, Ph.D. **Primary Examiner** 

Technology Center 1600